EXHIBIT 55

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Intraoperative Hypothermia and Surgical Site Infections in Patients with Class I/Clean Wounds: A Case-Control Study

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BACKGROUND: Numerous surgical quality metrics focus on prevention of unintentional perioperative hypothermia due, in part, to the association between hypothermia and surgical site infections (SSI). However, few studies have comprehensively evaluated the relationship between these metrics and SSI. In this study, we evaluated individual components of 1 set of hypothermia metrics to determine their association with SSI.

STUDY DESIGN: Patients with clean (class I) wounds who developed an SSI within 30 days after surgery, from January 2003 to December 2012, in 1 of 5 surgical specialties, were matched to specialty-specific controls without SSI. Stratified logistic regression models were used to assess the associations between (1) compliance with the Surgical Care Improvement Project (SCIP) Performance Measure, Surgery Patients with Perioperative Temperature Management (SCIP-Inf-10), overall and its components (maintenance of minimum body temperature and use of an active warming device) and SSI and (2) intraoperative hypothermia.

RESULTS: In both univariate and adjusted analyses using adjusted odds ratios (OR), SCIP-Inf-10 compliance was not associated with SSI (composite compliance OR 0.89, 95% CI 0.63 to 1.24; temperature compliance OR 0.92, 95% CI 0.78 to 1.09; forced-air warming device compliance OR 0.95, 95% CI 0.76 to 1.19). Higher intraoperative nadir temperature (OR 1.19, 95% CI 1.05 to 1.35) was associated with SSI. Percent of time exposed to a temperature $< 36°C$ (OR 0.98, 95% CI 0.96 to 1.01), and cumulative hypothermic exposure (°C*h $<36°C$) (OR 0.98, 95% CI 0.90 to 1.05) were not associated with SSI.

CONCLUSIONS: Intraoperative hypothermia was not significantly associated with SSI. These results suggest that development of compliance metrics may not be an effective strategy for SSI reduction in class I surgical wounds. (J Am Coll Surg 2017;224:160−171. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Surgical site infection (SSI) is associated with increased hospital length of stay, perioperative mortality, and higher cost of delivered care.[1-4] Unintentional perioperative hypothermia is common[5] and has been previously identified as a modifiable risk factor for SSI.[6-10] The Centers for Medicare and Medicaid Services (CMS) and Joint Commission's Surgical Care Improvement Project (SCIP) have previously endorsed a normothermia Performance Measure, Surgery Patients with Perioperative Temperature Management (SCIP-Inf-10), which required either a patient temperature greater than or equal to 36°C in the 30 minutes before or 15 minutes after the documented end of the anesthetic encounter, or intraoperative use of an active warming device. After endorsement, compliance rates with SCIP-Inf-10 neared 100%, and

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Abbreviations and Acronyms

DDQB = Data Discovery Query Builder
iAUC = incremental area under the curve
MCLSS = Mayo Clinic Life Science Services
OR = Odds ratio
SCIP-Inf-10 = Surgical Care Improvement Project Performance Measure, Surgery Patients with Perioperative Temperature Management
SSI = Surgical site infection

the differences between institutions were so small that the metric was retired by the Joint Commission in 2014. A related quality metric specifying postoperative normothermia has been proposed as a replacement.[11] Recent data, however, indicate that the association between perioperative hypothermia and SSI may not be as robust as previously reported.[12-16]

There are no evidence-based best practices for optimizing temperature management with the aim of preventing SSI. This is particularly true for class I, or clean surgical incision wounds, as they are the most common wound type, but have been under-represented compared with class II (clean/contaminated) wounds in previous SSI prevention studies. We conducted a retrospective case-control study that aimed to study SCIP Inf-10 compliance and evaluate the association between intraoperative hypothermia and SSI in a large multispecialty surgical population with class I/clean surgical wounds.

METHODS

Study design

After receiving approval from the Mayo Clinic Institutional Review Board and waived requirement for written informed consent, we conducted a single-center, retrospective, case-control study.

Study populations

All patients with class I/clean surgical wounds who developed SSI after a surgical intervention in 5 surgical specialties (general, neurologic, orthopaedic, spine, vascular), between January 2003 and December 2012, were identified from the Mayo Clinic Rochester, Division of Infectious Disease, Infection Prevention and Control (IPAC) SSI database. A class I/clean surgical wound was defined as "an uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage."[17] Surgical site infections were categorized as superficial, deep, or organ space, and were included if they occurred within 30 days of the index surgical procedure. An evaluation interval of 30 days was chosen to remain consistent with the SCIP-Inf-10's definition of SSI, and SSI cases were identified and validated via a dual review by infection control practitioners and an infectious disease physician specialist. Up to 3 controls were identified for each SSI case using the following criteria: age (±5 years), sex, American Society of Anesthesiologists Physical Status Classification (±1), date of surgery (±2 years), and Mayo Clinic Procedure Code. Mayo Clinic Procedure Code is internally defined and crosswalks national Current Procedural Terminology (CPT) codes. This procedure code is linked to the surgical specialty that performs the procedure, providing increased granularity and classification of the surgical procedure. Two different study populations were defined for the analysis of the relationship between SSI and SCIP-Inf-10 compliance (Fig. 1A) and SSI and intraoperative temperature (Fig. 1B).

The SCIP-Inf-10 does not define the modality or location of temperature measurement, so all types of temperature measurements were considered. The SCIP-Inf-10 study population included 1,335 SSI cases and 3,683 matched controls (Fig. 1A).

In contrast to the SCIP-Inf-10 analysis, for a subset analysis assessing the association between intraoperative temperature and SSI, only patients with temperature measurement locations consistent with core body temperature (esophageal, bladder, pulmonary artery catheter) were included. Additionally, any temperature value that changed 1°C in less than 4 minutes was identified by electronic algorithm, and these temperatures and those occurring 4 minutes before and after the identified temperature were reviewed independently by 2 authors (MD and AH). Single temperature values falling outside of an anticipated intraoperative trend were excluded. All manual reviews of temperature data and decisions regarding exclusions were made without knowledge of the patient's case or control status. Finally, only patients who had temperature data recorded for more than 66.7% of their operative procedures were included. For the SSI cases, 330 patients had inadequate or absent temperature data and were excluded along with their matched controls. In addition, 58 SSI cases were excluded due to the lack of a suitable control (inadequate or absent temperature data). The study population was evaluated further, and only cases (and their associated controls) who developed an SSI within 30 days of the index surgical procedure included. The final intraoperative hypothermic exposure study population consisted of 1,079 SSI cases and 2,549 controls (Fig. 1B).

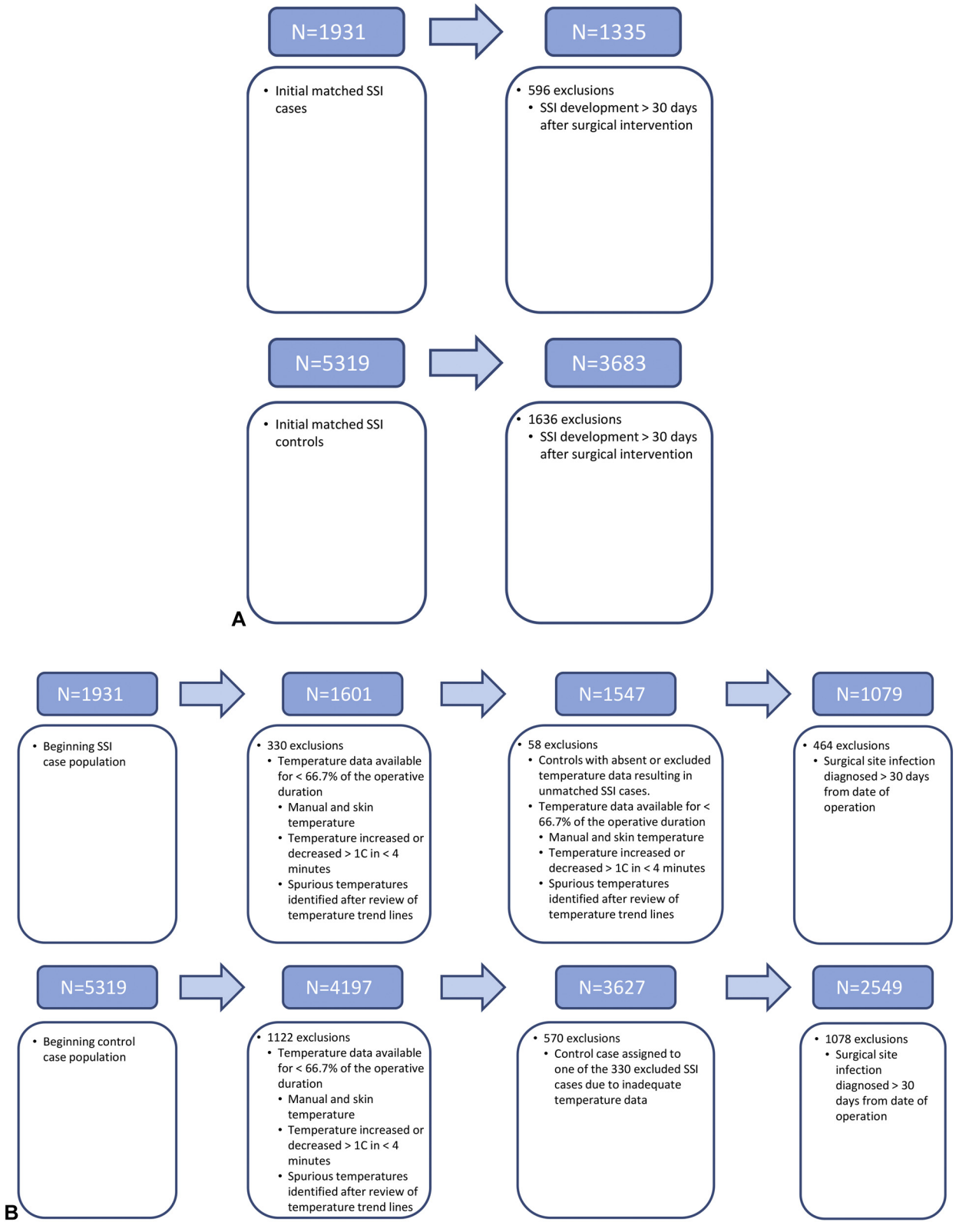

Figure 1. Perioperative hypothermic exposure and surgical site infection (SSI). (A) SCIP-Inf-10 study population: exclusion delineation. (B) Intraoperative hypothermic exposure population: exclusion delineation. SCIP-Inf-10, Surgical Care Improvement Project Performance Measure, Surgery Patients with Perioperative Temperature Management.

Baseline variables, clinical predictors, and study outcomes

Baseline demographic variables, clinical characteristics, comorbid conditions, procedural details, and specific risk factors previously associated with the development of SSI were extracted from the electronic health record (EHR) using data sources and tools described below. Risk factors for SSI included operative duration (defined as elapsed time between incision open to incision closed), timing of antibiotic administration, intraoperative blood component use (red blood cells [RBC], plasma and platelets), and BMI. The presence of comorbid conditions was quantified using the Charlson Comorbidity Index,[18] and individual coexiting disease processes, including diabetes mellitus, previous myocardial infarction, congestive heart failure, peripheral vascular disease, asthma, COPD, restrictive lung disease, cerebrovascular disease, cirrhosis, and renal disease were recorded. Hospital and ICU lengths of stay were collected for each patient.

For the SCIP-Inf-10 population, composite and individual SCIP-Inf-10 component compliance was determined. Patients without documented use of an active warming device were classified as noncompliant. Additionally, absence of a recorded temperature during the defined time period or those who had temperatures that failed to eclipse 36°C were classified as noncompliant.

For the intraoperative hypothermic exposure population, hypothermia was assessed in 3 distinct ways:

1. Hypothermic exposure measured in degree-hours calculated using incremental area under the curve (iAUC). The area below the reference line at 36°C and the tracing produced by 2-minute temperature sampling was computed using the trapezoidal rule. The iAUC was analyzed as a continuous variable and also stratified into 4 categories (none, 0.01 to 0.29, 0.30 to 0.89, and >0.90).
2. Nadir temperature, the lowest recorded temperature obtained during the observational period. Nadir temperatures were analyzed as a continuous variable and also grouped into 4 categories (≤34.9°C, 35.0°C to 35.4°C, 35.5°C to 35.9°C, ≥36.0°C).
3. The percentage of time the patient temperature was less than 36°C. This percentage was analyzed as a continuous variable and also grouped into 4 categories (0%, 1% to 29%, 30% to 74%, 75% to 100%).

Data sources

Data were collected from 2 primary sources: the Perioperative DataMart, and Mayo Clinic Life Science Services and the Data Discovery Query Builder (MCLSS/DDQB). The Perioperative DataMart is the access layer of an institutional data warehouse containing detailed information regarding most aspects of a patient's surgical encounter (eg demographic information, procedural descriptions, locations, start and stop times, detailed physiologic information including vital signs, ventilator data, laboratory information, and fluid, transfusion, and medication administration information).[19] The second primary data source (MCLSS/DDQB) has been previously described.[20,21] Briefly, MCLSS is a near real-time normalized replicate of the institution's electronic health record. This data warehouse is developed from multiple original clinical data sources, including highly annotated, full-text clinical notes, laboratory tests, diagnostic findings, demographics, and related clinical data from the year 2000 onward. The MCLSS also provides approved users with a query-building tool, the DDQB. The DDQB is a web-based application that is intended to help physicians and researchers interrogate data files contained in MCLSS. The DDQB allows users to identify administrative, demographic, laboratory, and diagnostic data of interest within the electronic health record. The accuracy of data obtained from this resource has been previously documented.[20,21]

Statistical analysis

Data are presented using mean ± SD or median with interquartile ranges for continuous variables and frequency percentages for categorical variables. Characteristics potentially associated with SSI were assessed using stratified logistic regression, taking into account the matched case-control study design. An overall analysis was performed using all SSI cases and controls (ie SCIP-Inf-10 population), and a subset analysis was performed for matched SSI cases and controls for whom intraoperative core temperature information was available (intraoperative hypothermic exposure population). For the overall analysis, the explanatory variables of interest were SCIP-Inf-10 compliance (overall, temperature, forced air warming) and for the subset analysis the explanatory variables of interest were iAUC below 36°C, the nadir temperature, and the percentage of time with temperature below 36°C. In addition to unadjusted analyses, multivariable stratified logistic regression was used to assesses the association between each explanatory variable of interest and SSI after adjusting for age, BMI, Charlson score, duration of surgery, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, asthma, COPD, interstitial lung disease, cerebrovascular disease, cirrhosis, moderate to severe renal disease, and any intraoperative requirement of red cells, platelets, or plasma. In all cases, findings are summarized using the odds ratio and corresponding 95% CI. Because SCIP-

Inf 10 was implemented during the study period, the chi-square test was used to assess whether the percentage of operations meeting compliance criteria differed between the time periods before and after SCIP-Inf 10 implementation. Two-tailed $p \leq 0.05$ was considered statistically significant. All statistical analyses were performed with SAS, version 9.3 (SAS Institute).

RESULTS

In both the SCIP-Inf-10 compliance and intraoperative hypothermic exposure populations, there were significant between-group differences in BMI; Charlson Comorbidity Index (including the individual components of diabetes mellitus, peripheral vascular disease, COPD, cirrhosis, and renal disease); duration of surgery, and exposure to RBC, platelet, and plasma transfusions for both populations (Tables 1 and 2).

Composite compliance with the SCIP Inf-10 clinical process of care measure significantly improved in the study population after its implementation as a reportable quality metric in October of 2009 (92% vs 99%, $p < 0.001$). Compliance with each individual component of SCIP-Inf-10 also improved after implementation as a quality measure (normothermia: 70% vs 82%, $p < 0.001$; use of a forced air warming device: 82% vs 94%, $p < 0.001$). In both SSI and control cases, end-of-case temperature documentation within the SCIP-Inf-10 acceptable time frame and documentation of an intraoperative forced-air (active) warming device improved after implementation of SCIP-Inf-10 (Table 3).

Compliance with the composite measure and the individual components of SCIP-Inf-10 was not significantly associated with reduced odds of SSI (Table 4). These findings were consistent in both the univariate and adjusted analyses. In the supplemental analyses evaluating specific surgical specialties, in the neurosurgery cohort only, composite SCIP-Inf-10 compliance (OR 0.28, 95% CI 0.10 to 0.84, $p = 0.023$), temperature compliance (OR 0.43, 95% CI 0.25 to 0.75, $p = 0.003$), and forced-air warming device documentation (OR 0.39, 95% CI 0.20 to 0.76, $p = 0.006$) were associated with reduced risk for SSI. Conversely, in the general surgery cohort, composite compliance (OR 3.08, 95% CI 1.23 to 7.71, $p = 0.017$) and forced-air warming device compliance (OR 2.01, 95% CI 1.19 to 3.41, $p = 0.010$) were associated with an increased odds of SSI. Temperature compliance only was associated with a reduced odds of SSI in the vascular surgery cohort (OR 0.60, 95% CI 0.37 to 0.97, $p = 0.036$).

The results of the analyses performed in the intraoperative hypothermic exposure population are presented in Table 5. In both univariate and adjusted analyses, intraoperative exposure to hypothermia measured in degree-hours (°C*h < 36°C), nadir temperature, and percent of surgical time less than 36°C were not associated with an increased risk for SSI. Conversely, higher nadir temperature, in both univariate (OR 1.20, 95% CI 1.07 to 1.35, $p = 0.002$) and adjusted analyses (OR 1.19, 95% CI 1.05 to 1.35, $p = 0.008$) was associated with an increased risk of SSI. The percent of time spent at less than 36°C was associated with a lower rate of SSI in univariate analysis (OR 0.97, 95% CI 0.95 to 0.99, $p = 0.006$), but had no impact on SSI in the adjusted analyses.

Supplemental sensitivity analyses evaluating individual surgical specialties are presented in Table 6. From these analyses, intraoperative hypothermic exposure, by any of the 3 measures, was not associated with an increased risk of SSI. In the general surgery (OR 1.42, 95% CI 1.07 to 1.87, $p < 0.05$) and neurosurgery subgroups (OR 1.53, 95% CI 1.02 to 2.29, $p < 0.05$), higher nadir temperature was associated with SSI.

DISCUSSION

The major finding of this study is the lack of an association between perioperative hypothermia and SSI in patients with class I/clean surgical wounds. These findings were robust and consistent using intraoperative and SCIP-Inf-10-defined end-of-case methods for evaluating the extent of hypothermia encountered. The results were also consistent across the majority of the sensitivity analyses performed. Despite biologic rationale suggesting impaired immune function in hypothermic conditions,[2,22-24] as well as clinical reports associating intraoperative hypothermia and SSI,[2,8-10] our results corroborate more recent investigations, indicating the lack of a significant association between perioperative hypothermia and SSI.[12-16]

Studies supporting an association between hypothermia and SSI have used a variety of definitions for hypothermia and single temperature measurement time points as variables to determine an association with SSI.[2,8-10,14] End-of-case temperature may not be an accurate reflection of intraoperative temperature exposure,[25] creating uncertainty and further ambiguity when attempting to determine an association between perioperative hypothermia exposure and SSI. Despite this, SCIP-Inf-10 used end-of-case temperature as 1 of its 2 criteria to determine compliance. We believe that a high national adherence rate with SCIP-Inf-10 was primarily due to the less labor intense documentation of forced-air warming device use as opposed to successful achievement of an end-of-case

Table 1. Demographics and Surgical Characteristics: SCIP-Inf-10 Population

Characteristic	SSI (n = 1,335)	Control (n = 3,683)	Odds ratio (95% CI)	p Value
Demographic and comorbidity				
Age, y, median (Q1, Q3)	60 (47, 72)	60 (48, 72)	—	—
Sex, n (%)				—
Male	680 (51)	1,866 (51)	—	
Female	655 (49)	1,817 (49)	—	
BMI, kg/m^2, median (Q1, Q3) (n = 4,737)	30.0 (25.9, 35.5)	28.7 (24.9, 33.4)	1.20 (1.15–1.26)	<0.001
ASA performance status, n (%)				—
1–2	599 (45)	1,674 (45)	—	
3–4	736 (55)	2,009 (55)	—	
Diabetes mellitus, n (%)	336 (25)	645 (18)	1.63 (1.39–1.92)	<0.001
Myocardial infarction, n (%)	126 (9)	299 (8)	1.17 (0.92–1.48)	0.20
Congestive heart failure, n (%)	84 (6)	178 (5)	1.35 (1.02–1.80)	0.039
Peripheral vascular disease, n (%)	117 (9)	198 (5)	1.88 (1.41–2.50)	<0.001
Asthma, n (%)	119 (9)	318 (9)	1.06 (0.85–1.33)	0.60
Obstructive lung disease, n (%)	122 (9)	241 (7)	1.50 (1.18–1.91)	<0.001
Interstitial lung disease, n (%)	11 (1)	32 (1)	0.93 (0.46–1.87)	0.84
Cerebrovascular disease, n (%)	108 (8)	224 (6)	1.37 (1.06–1.77)	0.015
Cirrhosis, n (%)	38 (3)	53 (1)	2.06 (1.34–3.16)	0.001
Moderate/severe renal disease, n (%)	152 (11)	323 (9)	1.40 (1.12–1.76)	0.003
Charlson morbidity score*	4 (2, 6)	4 (2, 6)	1.07 (1.04–1.10)	<0.001
Surgical characteristic				
Timing of surgery, n (%)				0.38
Before SCIP-10	870 (65)	2411 (65)	Ref.	
After SCIP-10	465 (35)	1272 (35)	1.15 (0.84–1.56)	
Surgical specialty, n (%)				—
General	278 (21)	803 (22)	—	
Neurosurgery	145 (11)	394 (11)	—	
Orthopaedic	507 (38)	1,384 (38)	—	
Spine	244 (18)	687 (19)	—	
Vascular	161 (12)	415 (11)	—	
Duration of surgery, min, median (Q1, Q3)	175 (105, 272)	149 (95, 238)	1.07 (1.05–1.09)	<0.001
Preincisional antibiotics, n (%)	986 (74)	2,773 (75)	0.91 (0.76–1.10)	0.35
Intraoperative transfusion				
Red cells administered, n (%)	239 (18)	502 (14)	1.43 (1.17–1.74)	<0.001
Volume of red cells administered (n = 741)	660 (331, 1,266)	650 (330, 900)	—	—
Platelets administered, n (%)	34 (3)	52 (1)	1.78 (1.14–2.80)	0.012
Volume of platelets administered, median (Q1, Q3), (n = 86)	292 (211, 589)	306 (219, 525)	—	—
Plasma administered, n (%)	41 (3)	62 (2)	1.83 (1.20–2.79)	0.005
Volume of plasma administered, median (Q1, Q3) (n = 103)	640 (529, 1,112)	600 (416, 1148)	—	—

Odds ratios, CI, and p values are from univariable stratified logistic regression. Comparisons were not performed for matching variables or volumes of intraoperative transfusions. Matching variables included age, sex, ASA performance status, date of surgery, and surgical procedure. Odds ratio for BMI reflects a 5-point increase, and OR for duration of surgery reflects a 30-minute increase.

*Mean ± SD was 4.6 ± 3.4 and 4.2 ± 3.1 for SSI and control patients, respectively.

ASA, American Society of Anesthesiologists; SCIP, Surgical Care Improvement Project; SSI, surgical site infection.

temperature greater than 36°C, leading to its retirement in 2014 as a quality measure. This is supported by our results suggesting that SCIP compliance was more frequently attained via forced-air warming device documentation (94%) than by reaching end-of-case normothermia (82%).

Table 2. Demographics and Surgical Characteristics: Intraoperative Hypothermic Exposure Population

Characteristic	SSI (n = 1,079)	Control (n = 2,549)	Odds ratio (95% CI)	p Value
Demographic and comorbidity				
Age, y, median (Q1, Q3)	60 (47, 72)	59 (47, 71)	—	—
Sex, n (%)				—
Male, n (%)	538 (50)	1,259 (49)	—	
Female, n (%)	541 (50)	1,290 (51)	—	
BMI, kg/m^2, median (Q1, Q3) (n = 3,413)	30.0 (25.9, 35.6)	28.4 (24.6, 33.1)	1.21 (1.15–1.28)	<0.001
ASA performance status, n (%)				—
1–2	469 (43)	1,110 (44)	—	
3–4	610 (57)	1,439 (56)	—	
Diabetes mellitus, n (%)	266 (25%)	427 (17)	1.68 (1.39–2.02)	<0.001
Myocardial infarction, n (%)	103 (10)	224 (9)	1.05 (0.80–1.37)	0.74
Congestive heart failure, n (%)	71 (7)	122 (5)	1.36 (0.98–1.87)	0.06
Peripheral vascular disease, n (%)	94 (9)	147 (6)	1.66 (1.21–2.29)	0.002
Asthma, n (%)	92 (9)	212 (8)	1.01 (0.78–1.32)	0.94
Obstructive lung disease, n (%)	99 (9)	170 (7)	1.44 (1.09–1.89)	0.010
Interstitial lung disease, n (%)	6 (1)	23 (1)	0.61 (0.24–1.52)	0.28
Cerebrovascular disease, n (%)	86 (8)	170 (7)	1.22 (0.92–1.63)	0.17
Cirrhosis, n (%)	29 (3)	34 (1)	2.24 (1.33–3.76)	0.002
Moderate/severe renal disease, n (%)	122 (11)	212 (8)	1.40 (1.08–1.80)	0.011
Charlson morbidity score, median (Q1, Q3)*	4 (2, 6)	4 (2, 6)	1.06 (1.02–1.09)	0.001
Surgical characteristic				
Timing of surgery, n (%)				0.62
Before SCIP–10	714 (66)	1,685 (66)	—	
After SCIP–10	365 (34)	864 (34)	1.09 (0.77–1.55)	
Surgical specialty, n (%)				—
General	242 (22)	600 (24)	—	
Neurosurgery	126 (12)	310 (12)	—	
Orthopaedic	345 (32)	728 (29)	—	
Spine	223 (21)	578 (23)	—	
Vascular	143 (13)	333 (13)	—	
Duration of surgery, min, median (Q1, Q3)	193 (115, 290)	172 (112, 267)	1.06 (1.04–1.08)	<.001
Preincisional antibiotics, n (%)	806 (75)	1,915 (75)	0.99 (0.80–1.23)	0.95
Intraoperative transfusion				
Red cells administered, n (%)	219 (20)	427 (17)	1.36 (1.10–1.68)	0.004
Volume of red cells administered, median (Q1, Q3) (n = 646)	660 (331, 1,300)	660 (330, 905)	—	—
Platelets administered, n (%)	32 (3)	45 (2)	1.79 (1.11–2.89)	0.016
Volume of platelets administered, median (Q1, Q3), (n = 77)	307 (214, 595)	300 (217, 526)	—	—
Plasma administered, n (%)	39 (4)	52 (2)	1.89 (1.21–2.94)	0.005
Volume of plasma administered, median (Q1, Q3), (n = 91)	640 (434, 1112)	600 (400, 1153)	—	—

Odds ratios, CI, and p values are from univariable stratified logistic regression. Comparisons were not performed for matching variables or volumes of intraoperative transfusions. Matching variables included age, sex, ASA performance status, date of surgery, and surgical procedure.
*Mean ± SD was 4.5 ± 3.3 and 4.3 ± 3.2 for SSI and control patients, respectively.
ASA, American Society of Anesthesiologists; SCIP, Surgical Care Improvement Project; SSI, surgical site infection.

A notable strength of this investigation is the more comprehensive assessment of perioperative hypothermic exposure. Specifically, in addition to end-of-case temperature, intraoperative nadir temperature as well as duration and "dose," as reported with the iAUC of hypothermic exposure, were evaluated. This methodology has

Table 3. SCIP-10 Performance Before and After Implementation of Clinical Process of Care Measure

Characteristic	Before SCIP-10 Total N	Before SCIP-10 n	Before SCIP-10 %	After SCIP-10 Total N	After SCIP-10 n	After SCIP-10 %	p Value*
Composite SCIP-10 compliance							
Overall	3,281	3,028	92	1,737	1,711	99	<0.001
SSI cases	870	805	93	465	457	98	<0.001
Controls	2,411	2,223	92	1,272	1,254	99	<0.001
Temperature compliant (≥36°C)†							
Overall	3,281	2,306	70	1,737	1,430	82	<0.001
SSI cases	870	599	69	465	378	81	<0.001
Controls	2,411	1,707	71	1,272	1,052	83	<0.001
Forced-air warming device documented							
Overall	3,281	2,700	82	1,737	1,640	94	<0.001
SSI cases	870	710	82	465	446	96	<0.001
Controls	2,411	1,990	83	1,272	1,194	94	<0.001

*p Values are from chi-square tests and do not account for matching.
†Noncompliance was defined as missing temperature documentation or temperature below 36°C. Temperature documentation was missing in 15% of patients before SCIP-10 and 10% of patients after SCIP-10.
SCIP, Surgical Care Improvement Project; SSI, surgical site infection.

Table 4. SCIP-10 Performance Metrics and Surgical Site Infection

Characteristic	SSI (n = 1,335) n	SSI (n = 1,335) %	Control (n = 3,683) n	Control (n = 3,683) %	Unadjusted analysis* OR (95% CI)	Unadjusted analysis* p Value	Adjusted analysis* OR (95% CI)	Adjusted analysis* p Value
Composite SCIP-10 compliance								
Overall	1,262	95	3,477	94	1.02 (0.75–1.38)	0.898	0.89 (0.63–1.24)	0.49
General surgery	269	97	744	93	2.62 (1.24–5.54)	0.012	3.08 (1.23–7.71)	0.017
Neurosurgery	135	93	380	96	0.42 (0.16–1.06)	0.066	0.28 (0.10–0.84)	0.023
Orthopaedic surgery	471	93	1,285	93	1.01 (0.64–1.58)	0.970	0.73 (0.43–1.23)	0.24
Spine surgery	236	97	675	98	0.46 (0.18–1.23)	0.122	0.48 (0.15–1.59)	0.23
Vascular surgery	151	94	393	95	0.80 (0.36–1.81)	0.594	0.79 (0.30–2.08)	0.64
Temperature compliant (≥36°C)								
Overall	977	73	2,759	75	0.90 (0.77–1.05)	0.183	0.92 (0.78–1.09)	0.35
General surgery	230	83	628	78	1.37 (0.95–1.99)	0.095	1.34 (0.88–2.03)	0.17
Neurosurgery	103	71	318	81	0.51 (0.30–0.84)	0.008	0.43 (0.25–0.75)	0.003
Orthopaedic surgery	356	70	958	69	1.04 (0.82–1.32)	0.738	1.03 (0.79–1.35)	0.82
Spine surgery	184	75	565	82	0.61 (0.42–0.90)	0.012	0.80 (0.50–1.26)	0.33
Vascular surgery	104	65	290	70	0.77 (0.51–1.15)	0.193	0.60 (0.37–0.97)	0.036
Forced-air warming device documented								
Overall	1,156	87	3,184	86	1.03 (0.84–1.27)	0.767	0.95 (0.76–1.19)	0.67
General surgery	250	90	664	83	2.20 (1.37–3.54)	0.001	2.01 (1.19–3.41)	0.010
Neurosurgery	119	82	354	90	0.47 (0.26–0.85)	0.013	0.39 (0.20–0.76)	0.006
Orthopaedic surgery	422	83	1,161	84	0.97 (0.70–1.33)	0.829	0.87 (0.61–1.24)	0.44
Spine surgery	221	91	643	94	0.65 (0.38–1.11)	0.113	0.68 (0.35–1.32)	0.26
Vascular surgery	144	89	362	87	1.28 (0.68–2.42)	0.453	1.25 (0.59–2.63)	0.57

*All estimates and p values are from stratified logistic regression. Odds ratios above 1 indicate an increased likelihood of SSI. Covariates included in the adjusted analyses were age, BMI, Charlson score, duration of surgery, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, asthma, COPD, interstitial lung disease, cerebrovascular disease, cirrhosis, moderate to severe renal disease, and any intraoperative requirement of RBCs, platelets, or plasma. Matching variables included age, sex, ASA performance status, date of surgery, and surgical procedure. Due to missing BMI information, 4,737 of 5,018 observations were used in the adjusted analyses (1,031 of 1,081 for general, 518 of 539 for neurosurgery, 1,757 of 1,891 for orthopaedic, 882 of 931 for spine, and 549 of 576 for vascular).
ASA, American Society of Anesthesiologists; OR, odds ratio; SCIP, Surgical Care Improvement Project; SSI, surgical site infection.

Table 5. Analysis of Intraoperative Temperature as a Risk Factor for Surgical Site Infection

			Unadjusted analysis		Adjusted analysis	
Characteristic	**SSI (n = 1,079)**	**Control (n = 2,549)**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
IAUC (°C per h < 36°C), mean ± SD	0.59 ± 1.19	0.60 ± 1.10	1.00 (0.93–1.07)	0.957	0.98 (0.90–1.05)	0.52
Categorical, n (%)				0.014		0.049
No hypothermia	412 (38)	861 (34)	Ref.		Ref.	
0.01–0.29	248 (23)	691 (27)	0.74 (0.61–0.89)		0.78 (0.63–0.95)	
0.30–0.89	208 (19)	464 (18)	0.93 (0.75–1.14)		0.98 (0.78–1.23)	
≥ 0.90	211 (20)	533 (21)	0.83 (0.67–1.03)		0.82 (0.64–1.04)	
Nadir temperature, °C, mean ± SD	35.7 ± 0.7	35.7 ± 0.7	1.20 (1.07–1.35)	0.002	1.19 (1.05–1.35)	0.008
Categorical, n (%)				0.037		0.18
≥ 36.0°	412 (38)	861 (34)	Ref.		Ref.	
35.5°–35.9°	341 (32)	858 (34)	0.82 (0.69–0.98)		0.83 (0.68–1.01)	
35.0°–35.4°	204 (19)	482 (19)	0.86 (0.69–1.07)		0.90 (0.71–1.14)	
≤ 34.9°	122 (11)	348 (14)	0.71 (0.56–0.92)		0.79 (0.60–1.04)	
Percentage of time below 36°C, mean ± SD	32 ± 36	35 ± 37	0.97 (0.95–0.99)*	0.006	0.98 (0.96–1.01)*	0.16
Categorical, n (%)				0.060		0.23
No hypothermia	412 (38)	861 (34)	Ref.		Ref.	
1%–29%	232 (22)	591 (23)	0.83 (0.67–1.01)		0.81 (0.65–1.01)	
30%–74%	231 (21)	571 (22)	0.84 (0.69–1.03)		0.84 (0.68–1.05)	
>75%	204 (19)	526 (21)	0.76 (0.61–0.95)		0.87 (0.69–1.11)	

Each temperature variable was assessed separately as both a continuous variable and categorically using the categories specified. Analyses were performed using stratified logistic regression, taking into account the matched case-control study design. Results are summarized using the odds ratio (OR) with corresponding 95% CI. Odds ratios above 1 indicate an increased likelihood of SSI. Covariates included in the adjusted analyses were age, BMI, Charlson Comorbidity Score, duration of surgery, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, asthma, obstructive lung disease, interstitial lung disease, cerebrovascular disease, cirrhosis moderate-severe renal disease, and any intraoperative requirement of red cells, platelets, or plasma. Matching variables included age, sex, ASA performance status, date of surgery, and surgical procedure. Due to missing BMI information, 3,413 of 3,628 observations were used in the adjusted analyses.

*When treated as a continuous variable, the OR estimates for the percentage of time below 36°C are for an increase of 10 percentage-points.

ASA, American Society of Anesthesiologists; IAUC, incremental area under the curve; OR, odds ratio; Ref, referent; SCIP, Surgical Care Improvement Project; SSI, surgical site infection.

been used to study the association between hypothermia and transfusion requirements,[5] and intraoperative hypotension and perioperative ischemic outcomes,[26] but to our knowledge, using a more comprehensive definition of hypothermia has not been previously used to study SSI.

Our results differ from those of studies that are frequently referenced in support of perioperative hypothermia as a quality measure. Notably, many of these previous studies were published well over a decade ago[6-10]; our patient population is more contemporary and spanned 2003 to 2012. During this timeframe, measures aimed at reducing SSI, such as preoperative hair removal via clipping (vs shaving),[27] preoperative antiseptic bathing,[28] and proper timing of antibiotic administration,[29] among others, have been reported in the literature, implemented as standard of care practices, and included as CMS Clinical Core Processes of Care measures. It is possible that these other measures aimed at reducing SSI obscured any effect of perioperative hypothermia avoidance.

The disparate association between SCIP-Inf-10 composite compliance and SSI in the neurosurgical and general surgery subgroups indicate that perioperative temperature management may have specialty specific benefits and/or detriments that remain unclear. Introducing a universal normothermia quality metric aimed at SSI reduction, without further investigation of these potential subspecialty differences, may lead to unintended adverse outcomes. The association between SCIP-Inf-10 composite compliance in the general surgery subgroup is an unexpected finding. Sensitivity analyses found SSI to be significantly associated with the use of forced-air warming devices in this subgroup. Though widely accepted as an effective intervention to maintain normothermia,[7] the data for its use are limited. A recent Cochrane review[30] of the effect of active warming on SSI found that only 3 studies, with a total of 589 participants, met criteria for inclusion and concluded that despite a beneficial effect, the level of evidence was low quality. Additionally, both simulation models and retrospective outcomes

Table 6. Sub-Group Analysis of Intraoperative Temperature as a Risk Factor for Surgical Site Infection

Characteristic	General OR (95% CI)	Neurosurgery OR (95% CI)	Spine OR (95% CI)	Vascular OR (95% CI)	Orthopaedic OR (95% CI)
IAUC (°C per hour < 36°C)	0.82 (0.66–1.02)	0.92 (0.72–1.17)	0.92 (0.74–1.14)	1.04 (0.88–1.23)	1.03 (0.90–1.18)
Categorical					
No hypothermia	Ref.	Ref.	Ref.	Ref.	Ref.
0.01 to 0.29	0.84 (0.55–1.27)	1.06 (0.52–2.13)	0.56 (0.34–0.92)*	1.09 (0.55–2.16)	0.67 (0.45–0.98)*
0.30 to 0.89	0.62 (0.37–1.06)	1.22 (0.63–2.36)	1.31 (0.78–2.18)	1.44 (0.75–2.76)	0.71 (0.45–1.13)
≥ 0.90	0.68 (0.41–1.14)	0.71 (0.35–1.45)	0.93 (0.54–1.60)	0.19 (0.63–2.25)	0.70 (0.43–1.16)
Nadir temperature (°C)	1.42 (1.07–1.87)*	1.53 (1.02–2.29)*	1.19 (0.88–1.60)	0.72 (0.50–1.05)	1.23 (0.97–1.57)
Categorical					
≥ 36.0°	Ref.	Ref.	Ref.	Ref.	Ref.
35.5° to 35.9°	0.74 (0.49–1.10)	1.16 (0.60–2.22)	0.70 (0.45–1.09)	1.19 (0.65–2.18)	0.74 (0.51–1.08)
35.0° to 35.4°	0.84 (0.50–1.42)	1.25 (0.63–2.46)	1.27 (0.76–2.13)	0.97 (0.50–1.87)	0.58 (0.36–0.94)*
≤ 34.9°	0.66 (0.37–1.19)	0.48 (0.20–1.17)	0.60 (0.29–1.23)	2.62 (1.18–5.80)	0.66 (0.38–1.12)
Percentage of time below 36°C	0.96 (0.91–1.00)	0.99 (0.92–1.07)	1.02 (0.96–1.08)	1.00 (0.94–1.08)	0.97 (0.93–1.01)
Categorical					
No hypothermia	Ref.	Ref.	Ref.	Ref.	Ref.
1% to 29%	0.90 (0.58–1.41)	0.92 (0.46–1.85)	0.64 (0.39–1.04)	1.28 (0.67–2.44)	0.65 (0.41–1.04)
30% to 74%	0.57 (0.35–0.93)*	0.99 (0.51–1.90)	0.96 (0.61–1.53)	1.33 (0.70–2.52)	0.70 (0.45–1.09)
>75%	0.76 (0.46–1.24)	1.06 (0.50–2.23)	1.03 (0.55–1.92)	1.13 (0.55–2.32)	0.70 (0.46–1.07)

Each temperature variable was assessed separately as both a continuous variable and categorically using the categories specified. Analyses were performed using stratified logistic regression, taking into account the matched case-control study design. Results are summarized using the OR with corresponding 95% CI. Odds ratios above 1 indicate an increased likelihood of SSI. Covariates included in the adjusted analyses were age, BMI, Charlson Comorbidity Score, duration of surgery, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, asthma, obstructive lung disease, interstitial lung disease, cerebrovascular disease, cirrhosis moderate-severe renal disease, and any intraoperative requirement of red cells, platelets, or plasma. Matching variables included age, sex, ASA performance status, date of surgery, and surgical procedure. Due to missing BMI information, 804 of 842 observations were used in the analysis for general surgery, 417 of 436 for neurosurgery, 763 of 801 for spine, 452 of 476 for vascular, and 977 of 1,073 for orthopaedic.
*p value < 0.05. For categorical variables, the multiple degree of freedom test (comparing across all groups simultaneously) was used.
ASA, American Society of Anesthesiologists; IAUC, incremental area under the curve; OR, odds ratio; Ref, referent; SCIP, Surgical Care Improvement Project; SSI, surgical site infection.

analyses have suggested that forced-air warming devices may disrupt ultra-clean operating room airflow, potentially contaminating the surgical field, with resultant risk for SSI.[31-33] Documentation of forced-air warming device location (upper body, lower body), initiation of airflow related to timing of surgical incision, fan speed, temperature setting of the device, and concealment of the device blanket are not components of our perioperative record, precluding a more detailed analysis of this association with SSI. Additionally, we cannot fully explain why the results seen in this subgroup did not manifest among the other surgical specialty subgroups. Regardless, the results of our study suggest that the application of a forced-air warming device should not be used as a performance metric until further evidence supporting its use becomes available.

Although this study did not associate intraoperative temperature management with SSI, we would not recommend cessation of efforts to prevent perioperative hypothermia. Maintenance of perioperative normothermia is likely a justifiable quality metric and desirable goal because increases in mortality, ischemic cardiovascular events,[15] blood component therapy,[5,34-36] and longer hospital length of stay[2] are associated with perioperative hypothermic exposure. However, our results suggest that continued tracking of SCIP-Inf-10 and intraoperative hypothermia exposure are not effective strategies for improving SSI rates, particularly in patients with class I wounds.

This study has a number of important strengths. The investigation included a large number of SSI cases with closely matched controls. The study further used innovative and validated electronic strategies (MCLSS/DDQB, Perioperative DataMart, Infection Prevention and Control) to ensure accurate identification of the study population with detailed characterization of their baseline demographics and clinical conditions as well as surgical exposures and associated physiologic responses.

Despite the robust nature of this study, it has limitations as well. This has the well-known limitation of a single center, retrospective study. As with all observational

investigations, confounding and bias are important considerations that we attempted to address as effectively as possible with the matched study design, restriction to class I/clean surgical wounds, rigorous statistical adjustments, and numerous sensitivity analyses. We did not match the SSI population to controls using all the accepted risk factors identified by the National Surgical Quality Improvement Program (NSQIP). However, in addition to our matching criteria (American Society of Anesthesiologists [ASA] status, male sex, and wound class), we adjusted for imbalances in most of the relevant measured variables (eg BMI, COPD, peripheral vascular disease, surgical duration, blood product administration). We adjusted for surgical complexity by including surgical subspecialty as a categorical variable, but we recognize that significant procedural heterogeneity within a surgical subspecialty may still exist. Additionally, although the length of surgical procedure did not significantly affect end-of-case temperature and achieving SCIP compliance, shorter surgical cases may have been less likely to use forced-air warming, and patients who were deemed to be at higher risk for SSI may have been more likely to be warmed. Statistical significance was identified in a limited number of categorical variables in the intraoperative hypothermia subgroup analysis; however, the clinical significance of these isolated findings is unknown and does not affect the conclusion of the manuscript. Finally, due to limitations of the databases used, the large size of our study participant cohort, and the retrospective nature of this study, we were unable to accurately gather data regarding more detailed aspects of perioperative temperature management (eg details relating to the efforts used to maintain intraoperative normothermia such as forced-air warming devices, fluid warming devices, room temperature settings, etc).

CONCLUSIONS

Intraoperative hypothermia was not associated with SSI in patients with class I surgical wounds. These results do not support the use of SCIP-10-Inf compliance or intraoperative hypothermic exposure as quality metrics or as tools to assess risk for SSI in patients with class I surgical wounds.

Author Contributions

Study conception and design: Brown, Curry, Schroeder, Hanson, Kor

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